Virchows Arch [Pathol Anat] (1984) 404:229–241

Virchows Archiv A

Immunohistochemical study on the liver in autopsy cases with disseminated intravascular coagulation (DIC) with reference to clinicopathological analysis

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Summary. Immunohistochemical and clinicopathological studies were performed in 27 autopsy cases with indisputable DIC, which had been selected from 1,800 autopsy cases of elderly people based on the following two criteria; 1. presence of fibrin thrombi in glomeruli, and 2. presence of fresh patchy necrotic foci in myocardium and/or fibrin thrombi in splenic sinuses. A high incidence of liver lesions (22/27) was revealed in autopsy cases with indisputable DIC. The liver lesions could be classified into four groups. Group-I (Central degeneration) was characterized by massive precipitation of fibrin irregularly around the central vein, causing parenchymal damage. Group-II (Central necrosis), showed coagulation necrosis in the cental zone due to circulatory disturbance caused by either shock as a cause of DIC or abrupt cessation of blood flow into the lobules following fibrin thrombus formation in vessels of Glisson's sheath. Both group-I and -II showed a short clinical duration of DIC. Group-III (Sinusoidal thrombosis), showed the presence of fibrin thrombi in sinusoids with mild parenchymal damage and long clinical duration of DIC. Group-IV (No thrombosis), showed neither parenchymal damage nor fibrin thrombi in sinusoids, but a long clinical duration of DIC.

Key words: Disseminated intravascular coagulation – Liver lesions – Thrombosis – Immunohistochemistry – Fibrin

Outstanding progress has been observed in recent physiological and biochemical studies on disseminated intravascular coagulation (DIC). DIC is frequently observed in aged people, who are suffering from two or more underlying diseases such as malignant neoplasia, urinary tract infection, pneumonia, sepsis and shock. There is still much controversy about the clinical

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diagnostic criteria of DIC (Colman et al. 1972; Al-Mondhiry 1975; Matsuda et al. 1977; Siegal et al. 1979; Spero et al. 1980), and definitive pathomorphological criteria have not been reported so far. Thus the statistical frequency of DIC differs with the criteria employed, but roughly estimated, DIC was observed in about 16–19% of autopsy cases in our hospital (Sugiura et al. 1977; Esaki et al. 1979). From the pathomorphological viewpoint, however, there are still many unsettled points. The liver is one of the important organs in the study of DIC, since it produces most of factors related to coagulation and fibrinolysis. In routine histological sections, the phosphotungstic acid-haematoxylin (PTAH) method is most commonly employed for detection of fibrin, although its specificity is still doubtful. In the present study, employing an indirect peroxidase antibody method which can specifically detect fibrin/fibrinogen and their degradation products, precise histochemical studies were made on liver of autopsy cases with indisputable DIC in Tokyo Metropolitan Geriatric Hospital.

Materials and methods

In the present study, 27 autopsy cases with indisputable DIC were selected from 1,800 cases autopsied in Tokyo Metropolitan Geriatric Hospital from 1974 to 1981. The twenty seven cases were composed of 7 males and 20 females and their average age was 74 years old (male) and 81 (females). The following criteria were employed for selection of 27 cases. –

1: Presence of definite fibrin thrombi in glomeruli.

2: Presence of either scattered foci of fresh patchy necrosis in myocardium or fibrin thrombi in splenic sinuses, or both.

Age, sex and underlying diseases of 27 cases were indicated in Table 1. Among these cases, there were no patients with viral/toxic hepatitis, but 2 cases had liver metastasis from gastrointestinal adenocarcinoma and one case, liver cirrhosis.

For routine histopathological examination, organs obtained at autopsy were fixed with 10% formalin, embedded in paraffin, sectioned at 4 μ and stained with haematoxylin-eosin, Azan Mallory, periodic acid-Schiff, elastica-van Gieson and phosphotungstic acid-haematoxylin (PTAH).

For indirect peroxidase antibody method, paraffin sections were deparaffinized, washed with phosphate-buffer saline (PBS, pH 7.2) and treated with 0.25% trypsin (Difco Lab. USA) in PBS at 37° C for 1 h, as previously reported (Eishi et al. 1981). The sections were placed in 0.3% H_2O_2 methanol solution for 30 min in order to eliminate endogenous or pseudoperoxidase activity and then washed with PBS. They were covered with normal non-immune, non-conjugated goat serum for 30 min in order to reduce the nonspecific background staining. The sections were then incubated with specific primary antisera for 30 min at room temperature, washed with PBS, then incubated with peroxidase-conjugated goat anti-rabbit immunoglobulin for 30 min and again washed with PBS. The sections were then reacted with Karnovsky's solution (0.05% 3,3′-diaminobenzidine tetrahydrochlorides and 0.01% H_2O_2 in Tris buffer, 0.05 M, pH 7.6) for 15 min and counterstained with 1% methylgreen for 1 h.

The following primary antisera were employed; i.e., rabbit anti-human fibrinogen, rabbit anti-human fibrinogen degradation products D and E, and rabbit anti-human platelets, all purchased from Behring Institute. All stainings were performed on serial sections and compared.

Results

Comparison of staining methods

By the indirect peroxidase antibody method, fibrin thrombi in the liver were positively stained in 22 of 27 cases (81%), and 15 out of these 22 positive cases were positively stained by PTAH. The magnitude of the positive reaction by PTAH was generally weaker than that by indirect peroxidase method (Fig. 1). There was no great difference in the pattern and positivity

Table 1. Examined cases

Case no.	Age and sex	Underlying diseases	Duration (prior to death) of			Other main pathological findings compatible with DIC
			DIC	Liver parenchymal		
				Damage	(Degree)	
I. Central degeneration						
1	77 f	Laryngeal ca, Lung meta	na	na	(—)	G M
2	78 f	Gastric ca, and bleeding, Shock	2 d	1 d	(+ + +)	G M I (P)
3	68 m	Lung squamous cell ca, Pneumonia	5 d	na	(—)	G M S B N
4	91 f	Duodenal papilla ca, and bleeding, Shock	3 d	2 d	(+ +)	G M N
5	72 m	Urinary bladder ca, UT infection, Sepsis, Shock	2 d	na	(—)	G M S N (P)
6	90 f	Pyelonephritis, Sepsis, Shock	4 d	(—)	(−)	G M S
7	75 m	Panperitonitis, Sepsis, Shock	6 d	2 d	(+)	G S B N (P)
8	82 f	Urinary bladder ca, Pyelonephritis	12 d	(—)	(−)	G M S B N (P)
II. Central necrosis						
9	68 m	Pyelonephritis, Pneumonia, Shock	5 d	5 d	(+ + +)	G M I
10	79 m	Pneumonia, Shock	3 d	na	(—)	G M B
11	79 f	Urinary bladder ca and operation, Shock	9 d	9 d	(+ + +)	G M B
12	72 f	Sick sinus syndrome, Pulmonary infarction	6 d	5 d	(+ + +)	G M (P)
13	81 f	Acute myocardial infarction, Shock	8 d	8 d	(+ +)	G M S B I
14	74 m	Lung adenoca, Shock	3 d	3 d	(+ + +)	G M S B N
15	75 f	Panperitonitis	9 d	4 d	(+ + +)	G M S (P)
III. Sinusoidal thrombosis						
16	79 f	Pyelonephritis, Sepsis, Shock	11 d	1 d	(+)	G M S B I (P)
17	74 f	Rectal ca, Liver and bone meta	1.5 m	(meta)	(+)	G M S I (P)
18	74 f	Lung squamous cell ca, Shock	na	(—)	(−)	G M S B N (P)
19	91 f	Cholelithiasis, Cholecystitis	1.5 m	na	(—)	G M S I (P)
20	79 f	Sigmoid colon ca	1 m	2 d	(+)	G S (P)
21	85 m	Gastric ca, Generalized lymph nodes meta	4 m	(—)	(−)	G M S B N (P)
22	77 f	Gastric ca, Liver and brain meta	2.5 m	(meta)	(+)	G M S (P)
IV. No thrombosis						
23	78 f	Gastric ca, Postoperative recurrence	5 m	(—)	(−)	G S
24	77 f	Subarachnoideal bleeding, Shock	1 m	(—)	(−)	G M S B N
25	92 f	UT infection, Sepsis, Shock	1 m	(—)	(−)	G M S
26	91 f	Purulent meningitis	na	(—)	(−)	G S N
27	84 f	Decubitus, Sepsis	1 m	(—)	(−)	G M S B

Abbreviations. ca, carcinoma; meta, metastasis; UT, urinary tract
na, not available, d, day(s); m, month(s)
G, glomerular thrombosis; M, fresh patchy necrosis in the myocardium; S, splenic sinus thrombosis; B, fresh cortical infarction of the brain; I, segmental ischaemic changes of the intestine; N, non-bacterial thrombotic endocarditis (NBTE); P, portal venule thrombosis in Glisson's sheath

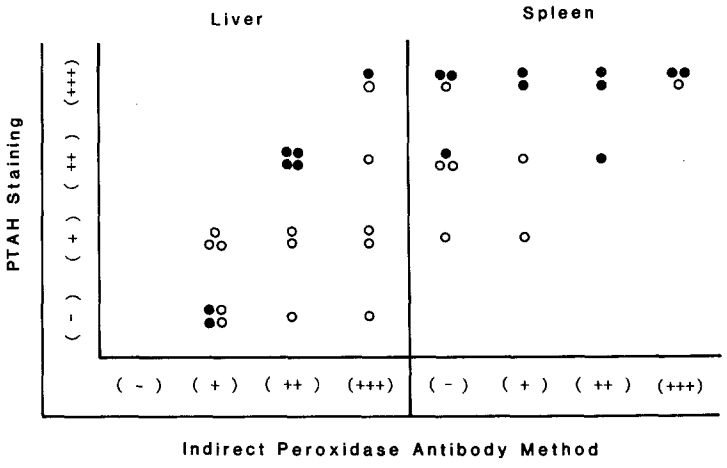

Fig. 1. Comparison of staining results of fibrin/fibrinogen and these derivatives between indirect peroxidase antibody method and PTAH staining. Staining intensity was expressed as grading of (−) to (+ + +). Open circles (o) show individual case with short clinical duration of DIC less than 10 days, and solid circles (•) that with long clinical duration. In the liver, the magnitude of the positive reaction by indirect peroxidase antibody method was generally stronger than that by PTAH staining, but in the spleen, vice versus

between indirect peroxidase methods using either antifibrinogen, anti-FDP-D or anti-FDP-E antibody in 16 of 22 cases (73%) (Fig. 2). In 4 cases, the staining intensity of FDP-D was different from that of fibrinogen and FDP-E. In 2 cases, the staining intensity of fibrinogen was weaker than that of FDP-D and FDP-E.

Using anti-platelet antibody, white thrombus in a relatively large vessel was stained positively, but fibrin thrombi, were negative. Thus in the present study, this anti-platelet antibody was employed as negative control for detection of fibrinogen derivatives.

Fibrin thrombi in the splenic sinuses and trabecular veins were positively stained by PTAH in 20 out of 27 cases (74%), and 12 out of these positive 20 cases were positively stained by indirect peroxidase method. In contrast with the results in the liver, the magnitude of the positive reaction by indirect peroxidase method was generally weaker than that by PTAH (Fig. 1).

Classification of liver lesions in DIC

From the immunohistochemical and the histopathological view points, the liver lesions of 27 cases were classified into the following 4 groups (Table 1).

Group-I (Central degeneration: 8/27 cases) was composed of focal degeneration of liver cells around central veins, although the shape and size were different in different cases. Most of the focal degeneration was situated irregularly and eccentrically around central veins and precipitation of various amount of fibrin was observed in and around degenerated liver cell cords. In severe cases, degenerating liver cell cords were embedded in massively precipitated fibrin (Fig. 3a). The staining of the degenerated portion

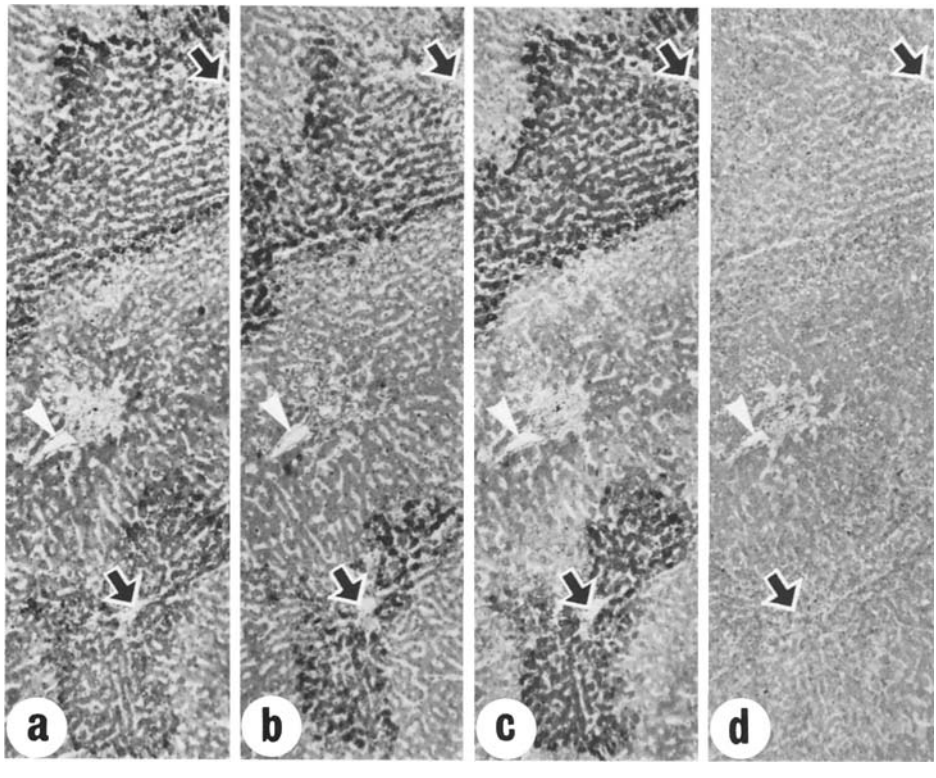

Fig. 2a–d. Immunohistochemical staining of fibrin/fibrinogen and these derivatives in the liver of Group-II, central necrosis. Comparison of staining pattern among four different antibodies; (**a**) anti-fibrinogen antibody, (**b**) anti-FDP-D antibody, (**c**) anti-FDP-E antibody and (**d**) anti-platelet antibody. Black arrows indicate central veins. White arrow, Glisson's sheath. Precipitation of fibrin was observed in the whole area of coagulation necrosis around the central veins and was especially prominent in the peripheral portion. No significant difference was observed among (**a**), (**b**) and (**c**). (**d**) was stained negatively. Case No. 10. × 54

with either haematoxylin-eosin or Azan Mallory showed a mottled appearance composed of red-stained precipitated fibrin and pale-stained degenerated liver cells. Macroscopically, the degenerated portion was invisible because of an ill-defined border. Fibrin thrombi were observed in portal venules of Glisson's sheath in 4 of 8 cases.

Group-II (Central necrosis: 7/27 cases) was composed of clear centrilobular necrosis around central veins. Necrotic foci could be observed even macroscopically, showing almost the same pattern as the liver change in cases of shock. Liver cells in the central zones showed coagulation necrosis with precipitation of fibrin in the whole area of necrosis, this was especially prominent in its peripheral portion (Fig. 2). There were occasionally fibrillar or fine granular fibrin thrombi and Kupffer cells ingesting fibrin in sinusoids around areas of necrosis. In 2 cases many fibrin thrombi were observed in portal venules in Glisson's sheath (Fig. 3b). The necrotic portion was

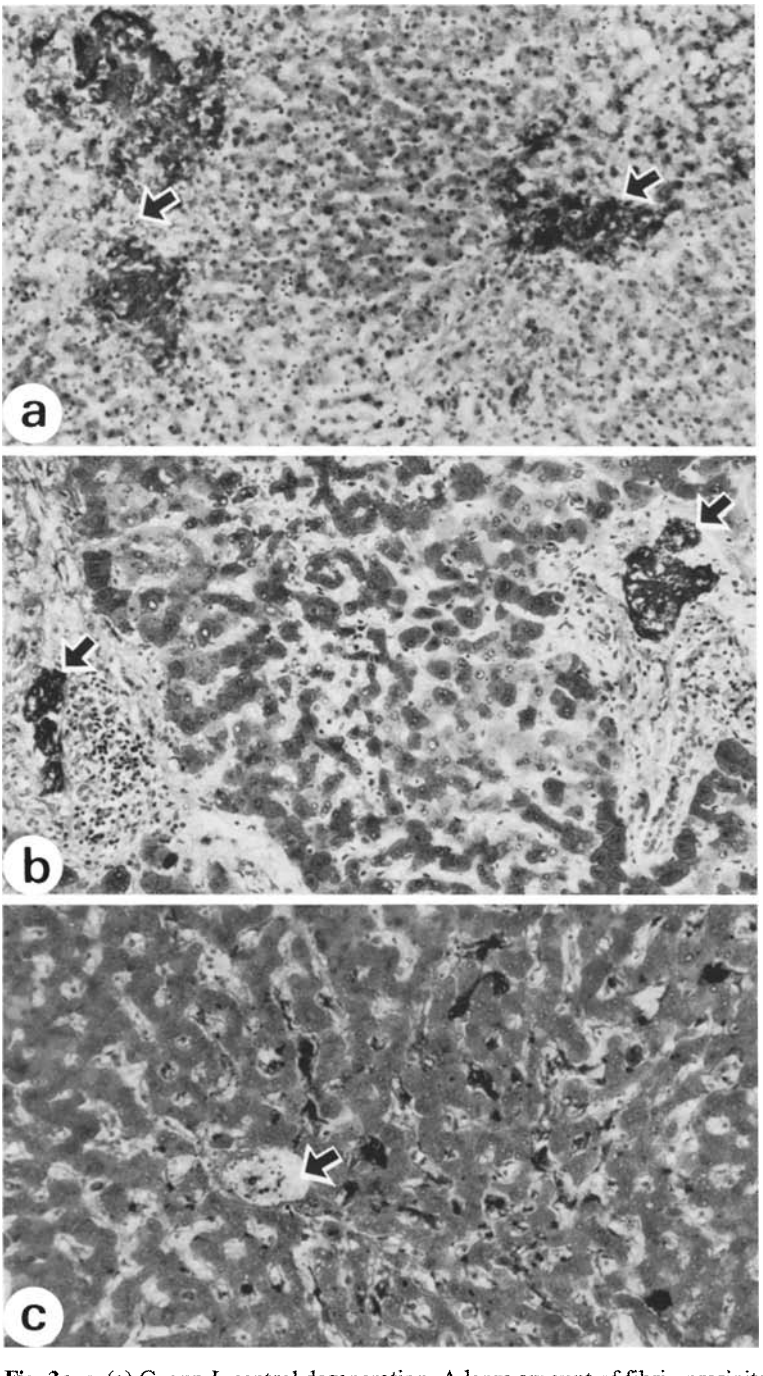

Fig. 3a–c. (**a**) Group-I, central degeneration. A large amount of fibrin precipitation was irregularly observed around central veins (arrows) with degeneration of liver cells. Case No. 8, stained with ati-FDP-D antibody. × 80. (**b**) Group-II, central necrosis. Fibrin thrombi (arrows) in the portal venules in the Glisson's sheaths. Case No. 12, stained with anti-FDP-D antibody, × 126. (**c**) Group-III, sinusoidal thrombosis. Scattered presence of microthrombi in sinusoids, Arrow indicates central vein. Case No. 16, stained with anti-fibrinogen antibody, × 135

Table 2. Other main pathological findings compatible with DIC

	Cases	Percentage
Kidney: Glomerular thrombosis	27	100
Myocardium: Fresh pathchy necrosis	23	85
Spleen: Sinusoidal thrombosis	20	74
Glisson's sheath: Portal thrombosis	13	48
Brain: Fresh cortical necrosis	12	44
Non-bacterial thrombotic endocarditis	10	37
Intestine: Segmental ischaemic changes	6	22

stained pale with a distinct border by haematoxilyn-eosin or Azan Mallory staining. There was no thrombosis detected in branches of hepatic artery in any case.

Group-III (Sinusoidal thrombosis: 7/27 cases) showed scattered presence of microthrombi in sinusoids and occasionally slight deposition of fibrin around liver cells of central zones (Fig. 3c). The number, shape and distribution of microthrombi were different in different cases. These crystalloid or coarse granular microthrombi showed fairly advanced organization of fibrin and were frequently stained by PTAH. In all cases, fibrin thrombi were also observed in portal venules of Glisson's sheath although few in number.

Group-IV (No thrombosis: 5/27 cases) showed neither formation of thrombus in any place within the liver, nor parenchymal damage.

Other main pathological findings compatible with DIC (Table 2)

Kidney. Fibrin thrombi in the renal glomeruli was observed in all cases examined in the present study although the degree of thrombus formation was different from case to case. In the severe cases No. 11, 15 and 20, extensive acute cortical necrosis was observed. All of the glomerular thrombi were already organized and were stained prominently by PTAH (Fig. 4a), but negative by the indirect peroxidase antibody method using anti-fibrinogen antiserum.

Heart. There were scattered foci of patchy fresh necrosis in myocardium (Fig. 4b) with or without microthrombosis in 23/27 cases in the present study. No significant difference was observed in the frequency of the myocardial lesion among 4 groups.

Non-bacterial thrombotic endocarditis (NBTE) was observed in 10/27 cases and there were no significant differences in frequency among 4 groups.

Spleen. Microthrombi were observed in sinuses and/or trabecular veins in 20/27 cases (Fig. 4c) and in several cases pulp cords were surrounded by

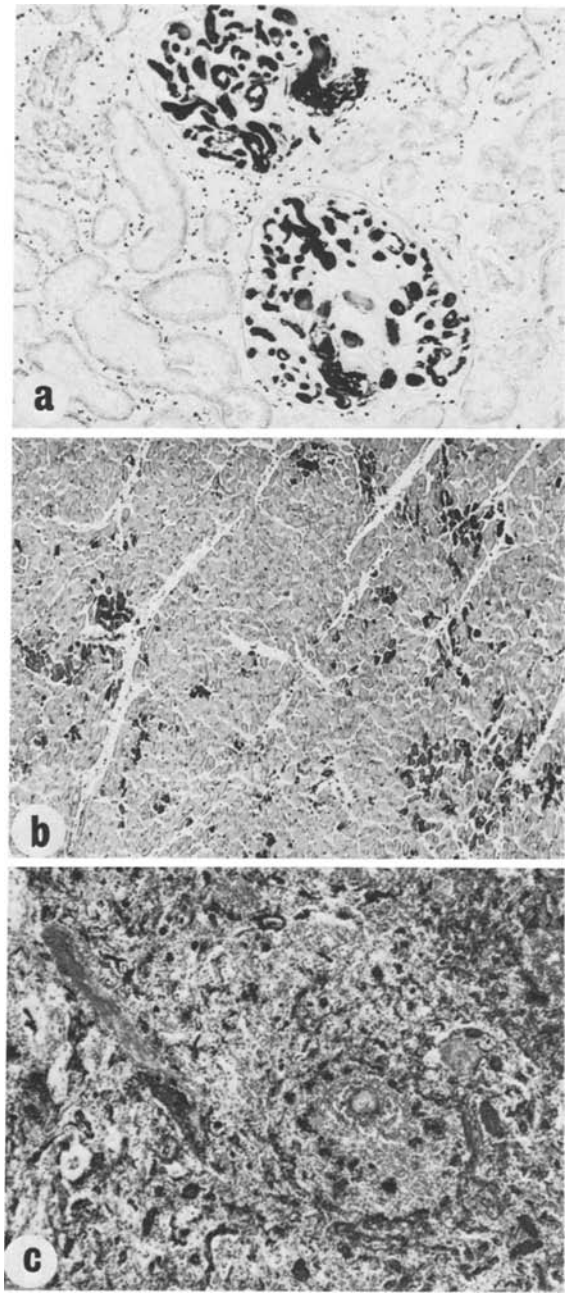

Fig. 4a–c. Findings compatible with DIC in other major organs. (**a**) Kidney; fibrin thrombi in glomeruli with advanced organization. Case No. 15, PTAH ×120. (**b**) Heart; scattered foci of patchy fresh necrosis in myocardium. Case No. 15, Azan Mallory, ×54. (**c**) Spleen; microthrombi in the sinus/trabecular vein. Case No. 20, stained with anti-fibrinogen antibody, ×54

precipitated fibrin. Fibrin thrombi in splenic sinuses and trabecular veins were observed in all cases which had a long duration of DIC, while in 7 out of 13 cases (54%) which had a shorter clinical duration of DIC less than 10 days. In the present study fresh splenic infarction was observed in 6 cases.

Table 3. Underlying diseases

Carcinoma	14 cases
Adenocarcinoma	8 cases
Squamous cell carcinoma	3 cases
Transitional cell carcinoma	3 cases
Infection	14 cases
(with Sepsis	6 cases)
Urinary tract	6 cases
Pneumonia	3 cases
Others	5 cases
Shock	14 cases
Others	7 cases
Sepsis and Shock	5 cases
Carcinoma and Metastasis	5 cases
Carcinoma and Infection	3 cases

Brain. There were scattered foci of fresh infarction in the cortex and subcortical medulla mainly of frontal and occipital lobes of the cerebrum as well as cerebellum (12/27 cases).

Intestine. Intestinal findings compatible with DIC were congestion, haemorrhage or necrosis appearing in a certain segment of intestinal wall and most frequently observed in ileocaecal portion, colon flexura and sigmoid colon (6/27 cases).

Underlying diseases of DIC (Table 3)

All patients with DIC, examined in the present study, had underlying diseases which were usually composed of a complex of chief, complicated and associated lesions; e.g., urinary tract infection followed by sepsis and shock in one case, and advanced carcinoma of the stomach followed by massive gastric haemorrhage and shock in the other case. Shock was observed in 14 of 27 cases and mostly common to Group-II.

Metastatic carcinoma of the liver was observed in two cases of Group-III, one from gastric cancer (Case No. 22) and the other from rectal cancer (Case No. 17). Liver cirrhosis was revealed in Case No. 23 of Group-IV at autopsy, although clinically asymptomatic.

Duration of DIC

In 24 of 27 cases, DIC was clinically diagnosed. Typical consumption coagulopathy which strongly suggested presence of DIC was generally observed in group-I and group-II and 93% (14/15) of them were clinically diagnosed as DIC. In group-III and group-IV, 83% (10/12) were clinically diagnosed as DIC. Clinical signs of DIC were bleeding symptoms, increased levels of serum FDP, decrease in plasma fibrinogen content and platelet count,

Table 4. Degree of liver parenchymal damage (Maximum unit of each case)

GPT	over 25 (+)	25– 53 (mean 42)
	over 100 (++)	104– 280 (mean 192)
	over 300 (+++)	649–1,500 (mean 1,018)
GOT	(+)	47– 176 (mean 96)
	(++)	114– 135 (mean 125)
	(+++)	400–2,360 (mean 1,160)
LDH	(+)	238– 679 (mean 437)
	(++)	265– 620 (mean 443)
	(+++)	698–2,370 (mean 1,516)

and prolongation of prothrombin time and retarded erythrocyte sedimentation rate. Duration of DIC was variable from case to case. In chronic cases, remission and relapse of DIC were occasionally observed during the course of the illness. Some cases showed a latent state and the other over-compensated state. After precise examination of laboratory data and clinical signs, duration of DIC occurred in the last stage of the illness was estimated (Table 1). About one half (13/27) of total cases died within 9 days after the occurrence of DIC. The duration of DIC was 2 to 12 days (average, 4 days) in group-I; within 9 days (average, 6 days) in group-II; apparently longer duration (average, about 2 months) in group III and group IV.

Liver parenchymal damage

The duration and degree of liver parenchymal damage occurring in the last stage of the illness was estimated from laboratory data. The degree was determined according to the maximum serum level of GPT; i.e., (+) over 25 units, (++) over 100 units, (+++) over 300 units. Serum levels of GOT and LDH were also taken into consideration, when determining the degree of the liver parenchymal damage (Table 1 and 4).

In group I, the duration of liver parenchymal damage in the terminal phase was at most 1 to 2 days, although the degree was variable. In most cases of group II, severe liver parenchymal damage was observed in association with clinical manifestation of DIC; i.e., development of abnormal coagulation findings appeared coincidentally with elevation of serum GPT in 4 of 7 cases. In group-III, the liver parenchymal damage was not observed or was marginal. No liver parenchymal damage was present in group-IV. In all cases, the level of laboratory data such as GPT, GOT and LDH was consistent with the degree of liver parenchymal damage at autopsy.

Discussion

A fibrinogen molecule is composed of 2 molecules of fragment D and one of fragment E when degradated by plasmic digestion and fibrin is composed of a variable number of fibrinogen polymer units (Marder and Budzynski

1974). The PTAH staining method, frequently used for fibrin was revealed to be suitable for organized fibrin molecules, but not for fibrin molecules during the process of either polymerization or degradation. In contrast, an indirect peroxidase antibody method using anti-fibrinogen, anti-FDP-D and anti-FDP-E antibodies was suitable for the latter, but not for the former. Therefore, for histological detection of fibrin thrombi in cases of DIC, not only PTAH staining but also immunohistochemical method should be employed.

In the present study, 27 cases of DIC were selected on the basis of strict criteria for DIC. In other words in addition to the 27 cases there were many cases of putative DIC, showing a similar pattern of liver lesions to that reported in this paper. One of typical features of DIC was observed in group-I, central degeneration; i.e., a large amount of fibrin produced in sinusoids surrounded liver cell cords resulting in secondary degeneration or necrosis of them. The duration of DIC before death in group I was short, 4 days in average, but this group may change to group-III or -IV, if survival follows the improvement of underlying disease. The most severe liver parenchymal damage was observed in group-II with defined laboratory data. In 5 of 7 cases of group-II, shock appeared to be a major underlying disease for DIC causing liver necrosis. In 2 of 7 cases of group-II, central necrosis of the liver was brought about by an abrupt cessation of portal blood flow due to massive formation of fibrin thrombi. Case 12 and 15, both in group II, appeared to belong to this type and numerous fibrin thrombi were observed in portal veins of Glisson's sheath (Fig. 3b), although the distribution and extent of necrotic foci were irregular. No shock was observed in the 2 cases in the terminal stages. There has been a case report of DIC in which focal or zonal necrosis coalesced resulting in submassive or massive necrosis of the liver (Aihara et al. 1982). In most cases of group-III, duration of DIC was long and the degree of liver parenchymal damage was slight. This is probably due to a smaller amount of fibrin formation in sinusoids, although the duration of DIC was long. Presence of group-IV indicated that liver lesion did not always occur in association with DIC. Fibrin thrombi in portal veins of Glisson's sheath and in splenic sinuses are considered to be produced in situ, but there is a possibility that the fibrin thrombi may be carried from the liver sinusoids, since reflux of blood flow may occur in DIC because of increase of blood viscosity.

Generally, the presence of fibrin thrombi in renal glomeruli was considered to be the most reliable pathological feature in DIC (Minna et al. 1974; Esaki et al. 1979). Scattered foci of fresh patchy necrosis in myocardium (Sugiura et al. 1977) and fibrin thrombi in splenic sinuses or trabecular veins were also significant findings in DIC.

Non-bacterial thrombotic endocarditis occurrs frequently in patients with DIC (Kim et al. 1977; Biller et al. 1982), and the verrucae on the valves are easily detached. Thus at autopsy, there were many cases in which embolism was observed in kidney, spleen, brain and intestine in spite of absence of verrucae on the cardiac valves.

Harms and Lehmann (1969) reported that shock occurred in 2/3 (102/153

cases) of autopsy cases with microthrombosis. Bleyl (1970, and 1971) also pointed out a causal relationship between shock and DIC in the pathogenesis of pulmonary hyaline membrane in the adult and newborn. Remmelle and Loeper (1973) reported that microthrombi were observed in about 17% of liver tissue of 171 cases with shock. These reports confirmed the presence of close relationship between shock and DIC.

Until recently, however, the direct relationship between the liver lesions and DIC could not be well documented, as it was difficult to detect fibrin thrombi clearly in the liver of autopsy cases of DIC. The liver lesions have been taken into consideration in relation to DIC chiefly in the following two aspects. One is that the criteria for diagnosis of DIC should differ depending upon whether liver lesions are present or not (Minna et al. 1974). The other is that the liver lesions themselves, especially in fulminant hepatitis, may cause DIC (Rake et al. 1970; Hillenbrand et al. 1974; Versdtraete et al. 1974). In the present study, however, we easily detected fibrin thrombi of varying amounts in the liver and it was revealed that a high incidence of liver lesions (22 out of 27 autopsy cases with DIC) could occur in relation to DIC. In 17 out of 22 cases, DIC was considered to be direct cause of the liver lesions.

Acknowledgements. We wish to thank Mrs. E. Mori-izumi for excellent technical help and Mr Y. Fujita for preparing the photographs.

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Accepted June 25, 1984